REMARKS

Upon entry of the foregoing amendment, claims 1-21 and 52-80 are pending in the application. Claims 22-51 were withdrawn by the Examiner under 37 C.F.R. § 1.142(b) as being directed to a non-elected invention and have been canceled without prejudice to, or disclaimer of, the material recited therein. Claims 1-21 and 52-80 were rejected under 35 U.S.C. § 103. Claims 75 and 80 are stated to be free of prior art. Applicants have not amended the claims, but provide a copy of the claims as currently pending for the Examiner's convenience.

The Rejection of the Claims Under 35 U.S.C. § 103 Is Traversed Or Rendered Moot

A. Prima Facie Obviousness

1. Claims 1-6, 8-10, 15-17, 52-53 and 61-62

The Examiner rejected claims 1-6, 8-10, 15-17, 52-53 and 61-62 as unpatentable under 35 U.S.C. § 103(a) in view of the combination of Cooper (U.S. Patent No. 5,719,055), Williamson et al., (Appl. Environ. Microbiol., 1994, 60:771-776), and Savakis et al., (U.S. Patent Publication 2003/0150007).

The Examiner cited Cooper as describing a vector encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase, an exogenous gene located between the transposon insertion sequences, and constitutive and/or inducible promoters regulating expression of the exogenous gene or the transposase. The Examiner cited Savakis et al. as describing the use of a modified transposon, where the modification includes disruption of transposase sequences or the incorporation of one or more heterologous coding sequences and/or expression control sequences, tissue-specific and/or inducible promoters, and that the sequence of the transposase may be modified to optimize codon usage and thus, increase transposition frequencies. Also, the Examiner cited Williamson et al. as describing modification of the 5' end of a prokaryotic gene to include a eukaryotic start codon and Kozak sequence. Office Action at pages 4-5.

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness. The Federal Circuit has stated that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and

use the apparatus or method." *Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989)). Also, subsection 706.02(j) of the MPEP states that to establish a prima facie case of obviousness three criteria must be met:

(i) a suggestion or motivation to modify or combine references;

(ii) a reasonable expectation of success; and

(iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references.

The Applicant respectfully asserts that the cited references do not describe each and every element of the claimed invention. Also, the cited references do not, alone or in combination, provide a motivation or suggestion to combine the references, or a reasonable expectation that such a combination would be successful for the reasons below.

The references fail to disclose elements of the claimed method

Applicants respectfully assert that the cited references do not, individually or in combination, teach or suggest a vector that uses a prokaryotic transposase gene (or any other prokaryotic gene) having a Kozak sequence as the first codon, and a transposase gene modified such that a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein are individually modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine, such that the modification does not change the amino acid encoded by the modified codon; and one or more genes of interest operably-linked to one or more additional promoters, wherein the one or more genes of interest and their operably-linked promoters are flanked by insertion sequences recognized by a transposase encoded by the modified transposase gene.

First, Savakis et al., does not describe a vector having transposon sequences and a transposase, but describes a method whereby transposon sequences are introduced into a first organism, the transposase is introduced into the second organism, and the animals are crossed to obtain transgenic progeny. Thus, although Savakis et al. does describe the use of transposase genes controlled by heterologous promoters, there is no teaching of

how to construct a vector having such elements as a single nucleic acid construct. Instead, the constructs of Savakis et al. require breeding and crossing of genetic progeny to produce cells having the transposase and the transposons in some of the same cells. The approach and vector constructs used by Savakis are very different that the constructs used by Applicants where both constructs are on the same vector, but differential control is provided by the combination of regulatory elements. Nor, do the constructs of Savakis display the high level of efficiency which is surprisingly seen with Applicants' constructs as discussed in detail below.

Also, although Savakis et al. mentions that the sequence of the transposase may be modified to optimize codon usage, Savakis et al. explicitly states that optimization of codon usage is defined as converting codons that are used less frequently in the transgenic host organism to codons that are used more frequently in the transgenic host organism. The optimization of codon usage that is described by Savakis et al. is distinct from Applicants' modification of the N-terminal first 10 codons to replace C or G at the wobble position with A or T. Applicants are not modifying the transposase to optimize codon usage for a particular host, but to increase strand dissociation during transcription. See the specification at pages 14-15. If Applicants were modifying the transposase to optimize codon usage (e.g., to change the codons usage to codons used in chickens), the change in codons would not provide a plurality of A or T's at the first 10 codons, but would modify codons throughout the gene to increase usage of codons used by the chicken or other host organism.

There is no expectation of success

Also, although Williamson et al. describes the use of a Kozak sequence to promote the initiation of translation in a eukaryotic system, Williamson also states that "the lysostaphin gene joins a small group of prokaryotic genes which are known to be expressed in mammalian cells." Williamson et al. at page 775, col. 2. Thus, one reading Williamson et al. would not expect to be successful in expressing a prokaryotic transposase gene in eukaryotic cells. Nor would one be motivated to attempt to express a prokaryotic transposase gene in a eukaryotic host *in vivo*.

There is no motivation or reason to combine the references

Furthermore, there is no motivation or reason to combine Cooper with Savakis et al. and Williamson et al. to arrive at Applicants' invention. As noted by the Examiner, the vectors of Cooper did not employ a Kozak sequence positioned so as to be included in at least the first codon of a prokaryotic transposase gene to promote translation of the prokaryotic transposae gene in eukaryotic cells. Nor did the vectors of Cooper employ a modified transposase gene as described and claimed by Applicants. As stated in Applicants' previous response filed September 26, 2006, Cooper does not render the vector of the invention obvious because Cooper teaches away from Applicants' vector. Thus, Cooper teaches that a transposase-based vector may be designed without the use of a Kozak sequence to promote translation of the prokaryotic transposase gene in eukaryotic cells. Cooper also teaches that a transposase-based vector may be designed without using a transposase gene that is modified from the wild-type sequence to include either an A or a T at the wobble position in a plurality of the first ten codons to promote strand dissociation of the transpose gene. The U.S. Supreme Court and the Federal Circuit have held that it is improper to combine references where the references teach away from their combination. See *KSR International Co., v. Teleflex Inc.*, 127 S.Ct. 1727, at 1739-1740 (2007); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Thus, one of skill in the art reading Cooper would not be motivated to incorporate a Kozak sequence in a transposon-based vector, or to include a modified transposase gene, as these modifications were not required for transformation of mammalian and/or fish cells as described in Cooper.

For the reasons stated above, Applicants respectfully assert the Examiner is relying upon hindsight provided by Applicant's specification in that combined references do not teach each and every limitation of the invention of claims 1-6, 8-10, 15-17, 52-53 and 61-62, and that there is no suggestion or motivation to combine the references, or an expectation of success that the elements can be combined to provide Applicants' claimed invention. Thus, Savakis et al. does not teach or suggest the modification of a prokaryotic transposase gene such that a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein are individually modified from the wild-type sequence of cytosine or guanine at the third base position of the codon

to an adenine or a thymine, such that the modification does not change the amino acid encoded by the modified codon. Savakis et al., does not describe, teach or suggest that one would modify the prokaryotic transposase gene in a manner to increase gene transcription, as Savakis only teaches codon optimization, which is used to increase protein translation. Also, Applicants respectfully assert that Cooper should not be used in combination with Williamson and/or Savakis to find claims 1-6, 8-10, 15-17, 52-53 and 61-62 unpatentable under 35 U.S.C. § 103(a) as Cooper teaches away from needing to modify the transposase gene, and does not provide any motivation to combine the references. Finally, reading Williamson et al., one would not have an expectation of success that a prokaryotic transposase gene could be used in a eukaryotic system. Thus, Applicants respectfully assert that without the hindsight provided by Applicants' application, the references of Cooper, Savakis et al., and Williamson et al. do not alone, or in combination, describe, teach or suggest the invention of claims 1-6, 8-10, 15-17, 52-53 and 61-62.

2. Claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79

The Examiner rejected claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 as unpatentable under 35 U.S.C. § 103(a) in view of the combination of Cooper, Williamson et al., and Savakis et al., further in view of Hackett et al., (U.S. Patent No. 6,489,458) and MacArthur et al. (U.S. Patent No. 6,825,396).

The Examiner stated that Cooper, Williamson et al. or Savakis et al. do not teach the advantage of using ovalbumin or other egg-directing sequences, but that MacArthur et al. describe a vector comprising control elements that include an enhanced promoter to direct the expression of a gene in the oviduct, a 5' untranslated sequence, a signal sequence directing secretion in the egg-white, control sequences for liver expression, a signal sequence for egg yolk, as well as standard stop codons and a polyA sequence 3' to the structural gene. The Examiner stated that MacArthur et al. does not describe the use of these elements with a transposon, but cited Hacket as disclosing use of promotors (including an ovalbumin promoter) to express a transgene.

The references fail to disclose elements of the claimed method

As recognized by the examiner, neither MacArthur et al., nor Hackett et al., disclose the use of eukaryotic promoters and signal sequences with a prokaryotic transposase. MacArthur et al. does not describe transposon-based vectors, but describes retroviral vectors that may be used to transfect an embryonic chicken cell, so as to produce a transgenic hen having the transgene expressed in the hen's oviduct and the protein produced in the hen's eggs or the eggs of her offspring. The promoters, signal sequences, and other control sequences described by MacArthur et al. are only used with the exogenous gene and are not used to control expression of a prokaryotic gene (e.g., a prokaryotic transposase) in a eukaryotic cell. Thus, there is no teaching in MacArthur et al. of how to use such sequences with a prokaryotic transposase gene as recited in Applicants' claims. Instead, the vectors of MacArthur et al. comprise a retroviral vector having an gene of interest under the control of elements known to be involved in protein production in egg white or egg yolk. Applicants note that MacArthur et al. describes the use of such vectors for the transfection of eggs for hatching and eventual production of G2 (second generation) transgenic animals. Thus, there is no teaching or suggestion in MacArthur et al. that such elements may be used to control the expression of a prokaryotic transposase gene in a eukaryotic cell, or how such elements may be combined to produce a vector that is able to generate G0 (original generation) chimeric animals.

Hackett et al. describes using the Sleeping Beauty family of eukaryotic transposases as a system for introducing nucleic acid into the genome of a vetebrate cell. Hackett et al. describes a series of experiments by which a transposase gene is reconstructed from inactive fragments (see Hackett at Example 1). Hackett et al. provides only a generic description that promoters and other regulatory elements may be used in transposon-based vectors. Hackett et al. does not, however, describe, teach, or suggest the specific nucleotide sequences of constitutive and inducible promoters, enhancer elements, and signal sequences that may be used for the transposase gene and the gene of interest, to allow for the targeted insertion and expression of a gene in particular cells as is provided by Applicants' claimed invention. In addition to the increased insertion frequencies provided by Applicants' vectors (see below), Applicants'

claimed vectors allow for versatility in selection of the gene of interest, as well as the tissue type in which the gene is expressed. For example, Applicants' vectors provide for using constitutive promoters to express the prokaryotic transposase (and thus insert the gene of interest) in all types of cells, in conjunction with inducible promoters (e.g., ovalbumin promoter and vitellogenin promoters) that may be used to direct the expressions of gene(s) of interest in specific cells or tissue types.

Nor do Hackett et al., or MacArthur et al. describe, teach or suggest a vector including a prokaryotic transposase having a Kozak sequence being positioned so as to include at least the first codon of the transposase gene, or that such a construct would be beneficial and provide increased expression of the transposase and/or integration of the construct in a eukaryotic genome. Also, there is also no mention in Hackett et al., or MacArthur et al., of modifying a prokaryotic transposase gene at the 5' end of the gene to have the third base position of the codon changed to an adenine or thymine at those positions where the change does not modify the amino acid encoded by the codon for increased strand dissociation and transcription of the prokaryotic transposase in eukaryotic cells.

There is no expectation of success

Also, in designing the SB transposase system, Hackett et al. does not describe, teach or suggest using a prokaryotic transposase for expression of a gene of interest in a eukaryotic system. In fact, Hackett et al. specifically teaches that most transposases are species-specific, and that only the (eukaryotic) Tc1/mariner superfamily of transposases would be expected to be useful for cross-species transposition. Hackett et al., at col. 2, lines 6-14.

There is no motivation to combine the references

Also, as noted above, there is no motivation provided by the references of Savakis et al., Williamson et al., or Cooper to modify a prokaryotic transposase gene in an attempt to create a vector for use in a eukaryotic system. Reading Williamson et al., one would be motivated to use a eukaryotic transposase for insertion of a gene of interest into eukaryotic cells. Also, reading Cooper, one would not be motivated to make modifications of the transposase gene as such modifications were not used in the vectors of Cooper. Also, Savakis et al., does not describe, teach or suggest that one would

modify the prokaryotic transposase gene in a manner to increase gene transcription, as Savakis only teaches codon optimization, which is used to increase protein translation. Thus, Applicants respectfully assert that without the hindsight provided by Applicants' application, the references of Cooper, Savakis et al., and Williamson et al., MacArthur et al., and Hackett et al., do not alone, or in combination, describe, teach or suggest the invention of claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79.

3. Claims 1-21, 52-74, 76, 78, and 79

The Examiner rejected claims 1-21, 52-74, 76, 78, and 79 as unpatentable under 35 U.S.C. § 103(a), in view of the combination of Cooper, Williamson et al., Savakis et al., Hackett et al., MacArthur et al., and Wallace et al. (Biology: The Science of Life, 1986, Scott Foresman and Company, page 235). The Examiner cited Wallace et al. as teaching the use of stop codons (UAA, UAG and UGA) and double stop codons. Office Action at page 9.

The references fail to disclose elements of the claimed method

Applicants respectfully assert that Wallace et al. does not correct the deficiencies of the references discussed above. Applicants' claimed vectors comprise a prokaryotic transposase gene operationally linked to a polyA sequence and/or two stop codons (claims 12, 14, 54, 56, and 63). There is no description, teaching or suggestion provided by Wallace et al. or other teachings (including MacArthur) in the art to include a polyA sequence that is operably-linked to a prokaryotic gene.

There is no expectation of success

The Examiner has asserted that "one of ordinary skill in the art . . . would have been motivated to include . . . polyA as a obvious modification for expression in mammalian system." Office Action at page 9. In fact, most prokaryotic genes do not include polyA sequences, and for the few prokaryotic genes that do include polyA sequences, the function of the polyA sequences is different than in eukaryotes. For these reasons, there was no expectation of success that a polyA sequence could be operably linked to a prokaryotic transposase gene and correctly positioned relative to the transposase gene and its associated stop codons. It was known in the art that improper positioning of the polyA sequence relative to a gene and its associated stop codons can

result in a decrease in mRNA stability, resulting in less protein being produced. Further, a review of the literature indicates that it has not been possible to predict what sequence elements downstream of the stop codon, other than the polyA, are involved in stability, again indicating that there was no inherent expectation of success that it would be possible to operably link a polyA sequence to a prokaryotic gene. Thus, one would not be motivated to rely on the use of polyA sequences to increase expression of a prokaryotic gene as it was not clear as to whether such an approach would be successful.

An invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Thus, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try," as for example, where the art gives only general guidance as to the particular form of the invention or how to achieve it. *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levengood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993). Applicants respectfully assert that without the hindsight provided by Applicants' application, the references of Cooper, Savakis et al., and Williamson et al., MacArthur et al., Hackett et al., and Wallace et al., do not alone, or in combination, describe, teach or suggest the invention of claims 1-21, 52-74, 76, 78, and 79. For at least these reasons, Applicants respectfully assert that pending claims 1-21, 52-74, 76, 78, and 79 are not *prima facie* obvious under 35 U.S.C. § 103, and respectfully request that the rejection be withdrawn.

B. Secondary Considerations

Additionally, secondary considerations render the claimed invention as not obvious over the cited references. The vectors of the present invention provide constructs that allow for the unexpected result of greatly improved expression of the transposase protein, thereby resulting in a significant increase in insertion frequencies. Applicants note that the vectors of the invention are far more efficient than vectors used in the prior art. Thus, as noted in the specification at page 13, lines 15-23, the vectors of the present invention produce integration frequencies an order of magnitude greater than other vectors commonly used at the time of the invention and almost a 2-fold increase in insertion frequency over the vectors of Cooper.

Additionally, Applicants' Declaration Under C.F.R. § 1.132, filed on September 26, 2006, showed that using a vector of the invention (pTnMod as described in Example 1 of the specification) with a monoclonal antibody encoded by the gene of interest resulted in very high efficiencies in transfecting both the livers and ovaries of female quails that were injected via a cardiac route. Applicants are not aware of any other vectors that approach this level of efficiency. The vectors used in the experiments described in the Declaration include a Kozak sequence positioned to include the first codon of the transposase, a modified transposase gene having a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine such that the modification does not change the amino acid encoded by the modified codon, as well as two stop codons, and a poly A sequence operably linked to the transposase.

Further, Applicants respectfully assert that it is the unique combination of elements provided by Applicants' vectors that enable the vectors to transfect cells in a live animal to produce chimeric animals in the G0 generation and expression of exogenous proteins in the egg white of eggs produced by the chimeric animal. Applicants are not aware of any other vectors that provide this capability. Applicants note that Cooper, MacArthur et al., and Hackett et al., each describe the use of such vectors for the direct transfection of eggs for hatching and eventual production of G2 transgenic animals. Thus, there is no teaching or suggestion in any of the cited references that such elements may be used to control the expression of a prokaryotic transposase gene in a eukaryotic cell, or how such elements may be combined to produce a vector that is able to generate G0 chimeric and/or G1 transgenic animals.

Thus, Applicants respectfully assert that claims 1-20 and 52-80 are not obvious under 35 U.S.C. § 103, and respectfully request that the rejection be withdrawn.

Notice of Other Applications

Applicants take this opportunity to bring to the Examiner's attention other applications that are being prosecuted in the United States and internationally for this invention and related technologies. Applicants will submit under separate cover a

supplemental Information Disclosure Statement, form SB/08A, and copies of correspondence in related international patent applications. As the same Examiner (Anoop Singh) is examining these patent applications in the U.S., Applicants bring to the Examiner's attention the office actions and responses that were filed in the following related U.S. Patent Applications: (A) 10/746,943 (Office Action mailed 02-13-2006; Response mailed 05-15-2006 (including interview summary); Office Action mailed 08-09-2006; Response mailed 10-10-2006; Advisory Action mailed 10-26-2006; RCE filed 12-08-2006; and Office Action mailed 03-06-2007); (B) 10/746,944 (Office Action mailed 02-10-2006; Response filed 05-10-2006 (including interview summary); Office Action mailed 07-27-2006; Response mailed 10-27-2006; Advisory Action mailed 11-07-2006; RCE filed 12-22-2006; and Office Action mailed 03-06-2007); (C) 10/746,149 (Office Action mailed 02-22-2006; Response filed 05-22-2006 (including interview summary); Office Action mailed 08-09-2006; Response filed 10-10-2006; Office Action mailed 10-26-2006; RCE filed 12-08-2006; Office Action mailed 02-28-2007); Supplemental IDS filed 07-30-2007; and Response filed 07-30-2007. Applicants also take this opportunity to bring to the Examiner's attention subsequently filed application 10/583,812 (filed June 22, 2006). It is Applicants understanding that the Examiner has access to these documents and as a courtesy to the Examiner, Applicants have not submitted additional copies of these documents at this time.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

Date: August 3, 2007

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I hereby certify that this correspondence is being electronically filed with the United States Patent Office via EFS Web, on August 3, 2007.

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